Relative Lipophilicities and Structural–Pharmacological Considerations of Various Angiotensin-Converting Enzyme (ACE) Inhibitors

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Received September 18, 1991; accepted April 23, 1992

Lipophilicities of seven structurally diverse angiotensin-converting enzyme (ACE) inhibitors, viz., captopril, zofenoprilat, enalaprilat, ramiprilat, lisinoprilat, fosinoprilat, and ceronaprilat (SQ29852), were compared by determining their octanol–water distribution coefficients (D) under physiological pH conditions. The distribution coefficients of zofenoprilat, enalaprilat, ramiprilat and fosinoprilat, which are the produg forms of zofenoprilat, enalaprilat, ramiprilat, and fosinoprilat, respectively, were also determined. Attempts were made to correlate lipophilicities with the reported data for oral absorption, protein binding, ACE inhibitory activity, propensity for biliary excretion, and penetration across the blood–brain barrier for these therapeutic entities. Better absorption of prodrugs compared to their respective active forms is in agreement with their greater lipophilicities. Captopril, lisinopril, and ceronapril are orally well absorbed despite their low lipophilicities, suggesting involvement of other factors such as a carrier-mediated transport process. Of all the compounds studied, the two most lipophilic ACE inhibitors, fosinoprilat and zofenoprilat, exhibit a rank-order correlation with respect to biliary excretion. This may explain the dual routes of elimination (renal and hepatic) observed with fosinoprilat in humans. The more lipophilic compounds also exhibit higher protein binding. Both the lipophilicity and a carrier-mediated process may be involved in penetration of some of these drugs into brain. For structurally similar compounds, in vitro ACE inhibitory activity increased with the increase in lipophilicity. However, no clear correlation between lipophilicity and ACE inhibitory activity emerged when different types of inhibitors are compared, possibly because their interactions with enzymes are primarily ionic in nature.

KEY WORDS: angiotensin-converting enzyme (ACE) inhibitors; lipophilicity; distribution coefficient; oral absorption; biliary excretion; structure–activity correlation.

INTRODUCTION

Since the discovery of captopril (1), angiotensin-converting enzyme (ACE) inhibitors have emerged as an important class of antihypertensive agents for the treatment of high blood pressure and congestive heart failure. Many ACE inhibitors have been approved for medical use or are in various stages of development (2). These compounds generally belong to three chemical categories, viz., sulfhydryl, carboxyalkyl dipeptide, and phosphorus-containing types (3).

These inhibitors differ in their rate and extent of oral absorption, duration of action, protein binding, mode of elimination, etc. (2). The inhibitors have also been differentiated by their selective inhibition of ACE in physiologically important target organs, such as aorta, heart, kidney, lung, serum, and brain (4). The possible difference in activity of ACE inhibitors in the brain attracted added attention after it was reported that ceronapril (SQ29852) and captopril increased adaptive and cognitive processes of learning and prevented scopolamine-induced impairment in mice (5), possibly by inducing central cholinergic activity.

The structure–activity relationships were studied by several investigators to explain differences among various ACE inhibitors (4,6,7). The lipophilicity plays an important role in membrane penetration, tissue and protein binding, etc. (8), and has been correlated with activities of various drug molecules (9,10). However, no systematic study on the relative lipophilicities of different ACE inhibitors has been reported. Ondetti (7) used octanol–water partition coefficient values which had been calculated theoretically in his structural relationship studies, and Gohike et al. (11) attempted to correlate lipophilicities of three ACE inhibitors of carboxyalkyl dipeptide type with their ability to penetrate the blood–brain barrier. It has also been suggested that lipophilicity may be a factor in the biliary excretion of certain ACE inhibitors (12,13). In the present study the octanol–water distribution coefficients under various pH conditions were determined for seven ACE inhibitors representing sulfhydryl, carboxyalkyl dipeptide, and phosphorus-containing types, and attempts made to correlate these with their reported oral absorption, enzyme inhibitory activity, plasma protein binding, mode of elimination, potential for crossing the blood–brain barrier, etc. The names and structures of the compounds studied are given in Fig. 1. Four of these inhibitors, namely, enalaprilat, fosinoprilat, ramiprilat and zofenoprilat are used clinically in prodrug forms. Therefore, the distribution coefficients of their prodrugs were also determined and considered in arriving at structure–activity relationships.

MATERIALS AND METHODS

Materials

Captopril, fosinopril sodium, fosinoprilat, zofenopril calcium, zofenoprilat (arginine salt), and ceronapril were produced by the Bristol-Myers Squibb Pharmaceutical Research Institute, Princeton, NJ. Enalaprilat, enalaprilat, and lisinopril were supplied by Merck & Co., Rahway, NJ, and ramipril and ramiprilat were supplied by Hoechst-Roussel Co., Somerville, NJ.

Determination of the Distribution Coefficient

The n-octanol–water distribution coefficients were determined in the pH range of 1 to 7 using the general procedure developed by Leo et al. (14). The aqueous media used
ACE Inhibitors

I. Sulphydryl Type

\[
\text{Captopril} \quad \text{Zofenopril} \\
\begin{array}{c}
\text{CH}_3 \\
\text{HS} - \text{CH}_2 - \text{CH} - \text{CO} - \text{N} - \text{COOH} \\
\end{array}
\begin{array}{c}
\text{CH}_3 \\
\text{HS} - \text{CH}_2 - \text{CH} - \text{CO} - \text{N} - \text{COOH} \\
\end{array}
\]

II. Carboxyalkyl Dipeptide Type

\[
\text{Enalaprilat} \quad \text{Enalapril} \\
\begin{array}{c}
\text{CH}_3 \\
\text{HOOC} - \text{CH} - \text{NH} - \text{CH} - \text{CO} - \text{N} - \text{COOH} \\
\end{array}
\begin{array}{c}
\text{CH}_3 \\
\text{HOOC} - \text{CH} - \text{NH} - \text{CH} - \text{CO} - \text{N} - \text{COOH} \\
\end{array}
\]

\[
\text{Ramiprilat} \quad \text{Ramipril} \\
\begin{array}{c}
\text{CH}_3 \\
\text{HOOC} - \text{CH} - \text{NH} - \text{CH} - \text{CO} - \text{N} - \text{COOH} \\
\end{array}
\begin{array}{c}
\text{CH}_3 \\
\text{HOOC} - \text{CH} - \text{NH} - \text{CH} - \text{CO} - \text{N} - \text{COOH} \\
\end{array}
\]

III. Phosphorus-containing Type

\[
\text{Fosinoprilat} \quad \text{Fosinopril} \\
\begin{array}{c}
\text{CH}_3 \\
\text{OH} \\
\text{CH}_2 - \text{CH} - \text{CO} - \text{N} - \text{COOH} \\
\end{array}
\begin{array}{c}
\text{CH}_3 \\
\text{OH} \\
\text{CH}_2 - \text{CH} - \text{CO} - \text{N} - \text{COOH} \\
\end{array}
\]

\[
\text{Cerepril} \\
\begin{array}{c}
\text{CH}_3 \\
\text{NH}_3 \\
\text{CH}_2 \\
\text{CH}_2 - \text{CH}_2 - \text{CH}_2 - \text{CO} - \text{N} - \text{COOH} \\
\end{array}
\begin{array}{c}
\text{CH}_3 \\
\text{OH} \\
\text{CH}_2 - \text{CH} - \text{CO} - \text{N} - \text{COOH} \\
\end{array}
\]

Fig. 1. Structures of ACE inhibitors and prodrugs used.